PS77 - The Study of Skin Permeation Mechanism and Terpene-Lipid Interaction via Nuclear Magnetic Resonance

Perry Fung Chye Lim [a], Xiang Yang Liu [b], Meng Huang [a], Paul Chi Lui Ho [a], Sui Yung Chan [a]

Department of Pharmacy [a], Department of Physics [b]

1. Introduction

The skin forms a formidable barrier against the percutaneous delivery of drugs. The protective quality of the skin is attributed to the unique composition and structural configuration of the intercellular stratum corneum (SC) lipids composed of ceramides, fatty acids, cholesterol and cholesterol esters.

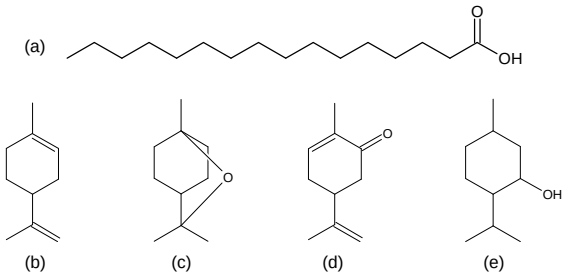

Fig 1. Chemical structures of (a) palmitic acid, and terpenes: (b) limonene (hydrocarbon); (c) cineole (oxide); (d) carvone (ketone); (e) menthol (alcohol).

Terpenes (Fig 1) as chemical skin enhancers have been found to intensify transdermal drug transport via several mechanisms elucidated using analytical techniques such as DSC and FTIR. These mechanisms include lipid fluidization, phase separation, lipid extraction, etc. In our case, the interaction between a terpene and a lipid was examined with nuclear magnetic resonance (NMR), which aims to provide some insight to enhancement in skin permeation.

2. Methods

^{1}H NMR spectra of terpenes (hydrocarbons, alcohols, ketones and oxides), palmitic acid and terpene-palmitic acid mixtures at different molar ratios in $CDCl_3$ were measured with Bruker Avance 300 spectrometer. Chemical shifts δ were recorded as units (ppm) relative to tetramethylsilane (TMS).

3. Results & Discussion

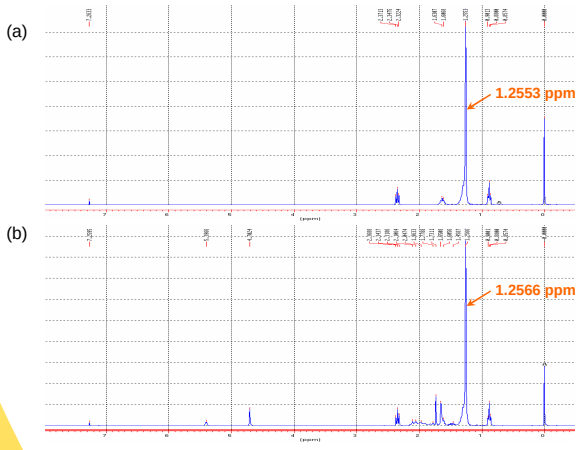

Fig 2. NMR spectra of (a) palmitic acid and (b) equimolar mixture of palmitic acid and limonene in $CDCl_3$ with TMS.

Palmitic acid (Fig 1), a 16-carbon fatty acid, was our model lipid. The rationale was changes in chemical shifts $\Delta\delta$ of the NMR spectrum of palmitic acid after terpene addition indicate some form of interaction between the two molecules.

Following terpene addition, the NMR signal corresponding to the lipid alkyl chain exhibited a $\Delta\delta$ ranging from 0.0013 to 0.0050 ppm (Fig 2, Table 1). The small $\Delta\delta$ was nonetheless significant, considering the high sensitivity and reproducibility of NMR spectroscopy. Hydrocarbons and ketones relative to alcohols and oxides were able to produce a greater $\Delta\delta$.

Table 1. Changes in chemical shift $\Delta\delta$ of the alkyl chain NMR signal of palmitic acid (lipid) following enhancer addition at different enhancer:lipid molar ratios.

			Enhancer:Lipid Molar Ratio					
			1:1		3:1		5:1	
Enhancer	**Class**	**log *P*** [a]	δ (ppm)	$\Delta\delta$ [b] (ppm)	δ (ppm)	$\Delta\delta$ [b] (ppm)	δ (ppm)	$\Delta\delta$ [b] (ppm)
Linalool	Alcohol	2.97	1.2566	0.0013	1.2566	0.0013	1.2591	0.0038
Menthol	Alcohol	3.30	1.2566	0.0013	1.2578	0.0025	1.2578	0.0025
Terpineol	Alcohol	3.33	1.2566	0.0013	1.2566	0.0013	1.2578	0.0025
Limonene	Hydrocarbon	4.83	1.2566	0.0013	1.2578	0.0025	1.2603	0.0050
Terpinolene	Hydrocarbon	4.47	1.2566	0.0013	1.2591	0.0038	1.2591	0.0038
Cineole	Oxide	2.50	1.2566	0.0013	1.2566	0.0013	1.2578	0.0025
Limonene oxide	Oxide	3.43	1.2566	0.0013	1.2578	0.0025	1.2591	0.0038
Pinene oxide	Oxide	2.87	1.2566	0.0013	1.2578	0.0025	1.2578	0.0025
Carvone	Ketone	3.07	1.2566	0.0013	1.2578	0.0025	1.2591	0.0038
Pulegone	Ketone	3.20	1.2578	0.0025	1.2591	0.0038	1.2591	0.0038
PG [c]	Alcohol	-0.92	1.2553	0	1.2566	0.0013	1.2553	0

[a] log *P* obtained from Howard and Meylan, *Handbook of Physical Properties of Organic chemicals*, 1997.
[b] $\Delta\delta = \delta - 1.2553$
[c] PG: propylene glycol

Propylene glycol (PG) is a common vehicle and it was reported that PG by itself exerted some enhancing property. This was demonstrated to a certain extent as Table 1 shows that PG elicited a $\Delta\delta$ at a PG:lipid molar ratio of 3:1 There was also a positive correlation between $\Delta\delta$ of the alkyl chain NMR signal and log *P* of the enhancer (Fig 3), and a better correlation fit was obtained at a higher enhancer:lipid molar ratio.

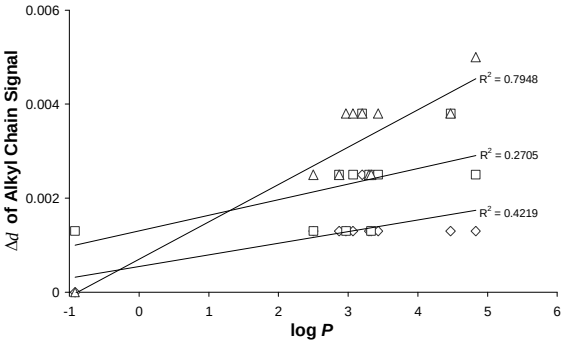

Fig 3. Change in chemical shift $\Delta\delta$ of the alkyl chain NMR signal of palmitic acid (lipid) following enhancer addition against log *P* of enhancer at different enhancer:lipid molar ratios of 1:1 (◊), 3:1 (□) and 5:1(△).

4. Conclusion

Based on NMR results, the terpenes associate with palmitic acid, probably via hydrophobic interaction. Hydrocarbon terpenes with their high lipophilities would be able to partition in a larger amount into the hydrocarbon interior of the SC lipid lamellae and interact more strongly with the hydrocarbon chains, hence disrupting and reorganizing the ordered lipoidal packing to a greater extent. This could account for an enhanced permeation for both hydrophilic and hydrophobic drugs observed by others.